Different profile of cytokine synthesis according to the severity of acute pancreatitis.


Department of Gastroenterology, Hospital General Universitario de Alicante, Pintor Baeza s/n. Alicante, Spain.

The authors aimed to evaluate the cellular synthetic ability of cytokines involved in pro- and anti-inflammatory reactions in patients with acute pancreatitis. Sixty-seven patients with acute pancreatitis (16 severe, 51 mild) and 10 controls were included in the study. Cultures of whole blood were performed in samples obtained within the first 72 h from the onset of pain. Serum levels of interleukins 6, 8, 10, and TNF-alpha were measured at baseline and in the supernatant of cultures with or without stimulation with phytohemaglutinin. Basal levels of cytokines were significantly higher in patients with severe acute pancreatitis. A significant increase of all pro-inflammatory cytokines vs. basal levels was observed in the supernatant after 24 h of whole blood cultures in patients, but not in controls. In contrast, interleukin 10 increased significantly in the supernatant of cultures only in patients with mild acute pancreatitis. Cells showed a statistically significant functional reserve for all interleukins in patients with mild, but only for pro-inflammatory cytokines in patients with severe acute pancreatitis. In conclusion, a marked activation of immune system may be observed in patients with severe acute pancreatitis, which might lead to a worst prognosis.

The cannabinoid 1 receptor antagonist, AM251, prolongs the survival of rats with severe acute pancreatitis.


Division of Gastroenterological Surgery, Tohoku University Graduate School of Medicine. Aoba-ku, Sendai, Japan.

It has recently been recognized that anandamide (arachidonylethanolamide), which is an endogeneous-cannabinoid (endocannabinoid), mediates septic shock. Cannabinoid means a mind-active material in cannabis (marijuana). Anandamide is mainly produced by macrophages. Cannabinoid 1 (CB1) receptor, which is one of the cannabinoid receptors, is also known to mediate hypotensive shock. The role of endocannabinoids in the progression of acute pancreatitis is unclear. The aims of this study are to clarify their relationship and to find a new therapeutic strategy by regulating the endocannabinoid signaling in acute pancreatitis. Male Wistar rats were injected with caerulein intravenously to induce mild edematous pancreatitis or injected with 5% sodium taurocholate to the bilio-pancreatic duct to induce severe necrotizing pancreatitis. The animals in the latter group were also injected with a CB1 receptor antagonist, AM251, or vehicle solution to see if the inhibition of endocannabinoids improves their survival. Plasma anandamide level was measured by the liquid chromatography/tandem mass spectrometry method. In both models of acute pancreatitis, the plasma anandamide levels were increased, and the
levels were significantly higher in rats with severe necrotizing pancreatitis than those in rats with mild edematous pancreatitis. The mean arterial pressure and survival rate were significantly improved by the treatment with AM251, despite that the local inflammatory changes in the pancreas and various parameters (white blood cells, hematocrit, serum amylase, and serum interleukin-6) were similar. The authors showed that endocannabinoids are involved in the deterioration of acute pancreatitis and that the down-regulation of endocannabinoid signaling may be a new therapeutic strategy for severe acute pancreatitis.


Systematic appraisal of the management of the major vascular complications of pancreatitis.

Balachandra S, Siriwardena AK.

Hepatobiliary Unit, Department of Surgery, Manchester Royal Infirmary, Manchester, United Kingdom.

This study is a systematic appraisal of the management of major vascular complications of pancreatitis conducted by collating individual patient-episode data from published literature. Searches identified 79 papers of which 62 provided detailed information on the clinical course of 214 patients. Principal outcomes were modes of presentation, results of diagnostic angiography, and embolization and overall outcome. There were 160 "spontaneous" and 40 postoperative episodes of hemorrhage. Underlying pancreatic disease was chronic pancreatitis in 40 patients, pseudocyst in 135 patients, and acute pancreatitis in the remaining 39 patients. Angiography was undertaken in 173 (81%) with embolization attempted in 115 and achieving hemostasis in 85 (75%). There were 40 (19%) deaths. Mortality was greater in patients undergoing surgery as first intervention compared with angiography first (P=0.01). This analysis of pooled data provides evidence of a central role for mesenteric angiography in the diagnosis of major vascular complications of pancreatitis and for angiographic embolization as a powerful tool for achieving hemostasis.


Risk factors and outcomes of pancreatitis after open heart surgery.

Perez A, Ito H, Farivar RS, Cohn LH, Byrne JG, Rawn JD, et al.

Department of Surgery, Brigham and Women's Hospital, Harvard Medical School. Boston, MA, USA.

The authors sought to analyze the risk factors and natural history associated with post-cardiac surgery acute pancreatitis. Retrospective analysis of all patients having undergone cardiac surgery at our hospital between January 1, 1992, and October 1, 2001. A total of 10,249 cardiac operations were performed. Thirty-nine (0.4%) patients developed postoperative pancreatitis. There was a higher incidence during the period spanning 1992 through 1996 than 1997 through 2001 (0.6% versus 0.2%, P<0.05). Patients with pancreatitis had longer postoperative length of stay (51±5 days versus 10±1 days, P<0.05) and a greater in-hospital mortality rate (28% versus 4%, P<0.05) than patients who did not develop pancreatitis. A history of alcohol abuse, cardiac surgery performed during 1992 to 1996, increased cardiopulmonary bypass time, and increased cross-clamp time were independent risk factors for the development of pancreatitis. Multiple-organ failure was an independent predictor for death among patients with pancreatitis. In conclusions, although the frequency of post-cardiac surgery pancreatitis is diminishing, it is still associated with significant mortality.
Neutral endopeptidase determines the severity of pancreatitis-associated lung injury.

Day AL, Wick E, Jordan TH, Jaffray CE, Bunnett NW, Grady EF, Kirkwood KS.

Department of Surgery, University of California. San Francisco, CA, USA.

Neutral endopeptidase (NEP) is a cell-surface metalloprotease that degrades proinflammatory peptides such as substance P, neurokinin A, and bradykinin. Inhibition of NEP exacerbates both experimental pancreatitis and the associated lung injury. It is unclear if worsened lung injury is the indirect result of more severe pancreatitis or if it is a direct effect of NEP inhibition in the lung. The authors used a model of pancreatitis-associated lung injury (PALI) to test the hypothesis that antagonism or genetic deletion of NEP augments PALI inflammation and pulmonary damage irregardless of the degree of pancreatic inflammation. In NEP(+/+) mice, intraperitoneal injection of porcine pancreatic elastase (elastase, 0.085 U/g at t=0 h and t=1 h) caused a 7-fold increase in lung myeloperoxidase (MPO) activity and marked pulmonary edema, neutrophil infiltration, and hemorrhage at 4 h as compared to control animals. The pattern of lung injury induced by elastase mimicked that observed among a separate group of animals with PALI induced by cerulein but was not associated with pancreatitis. Both NEP(-/-) mice and NEP(+/-) mice pretreated with the NEP antagonist phosphoramidon (10 mg/kg s.c.) had significant elevations of lung MPO and worsened lung histology compared to NEP(+/-) mice given elastase alone. Antagonism of either the vanilloid receptor transient receptor vanilloid 1 or the substance P receptor NK1-R had no effect on elastase-mediated lung injury in NEP-deficient mice. In conclusion, NEP is an inhibitor of pancreatic elastase-induced lung injury, presumably via degradation of proinflammatory mediators.

Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study.

Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN.

Cancer Research Center of Hawaii. Honolulu, HI, USA.

Meat intake has been associated with risk of exocrine pancreatic cancer, but previous findings have been inconsistent. This association has been attributed to both the fat and cholesterol content of meats and to food preparation methods. The authors analyzed data from the prospective Multiethnic Cohort Study to investigate associations between intake of meat, other animal products, fat, and cholesterol and pancreatic cancer risk. During 7 years of follow-up, 482 incident pancreatic cancers occurred in 190,545 cohort members. Dietary intake was assessed using a quantitative food frequency questionnaire. Associations for foods and nutrients relative to total energy intake were determined by Cox proportional hazards models stratified by gender and time on study and adjusted for age, smoking status, history of diabetes mellitus and familial pancreatic cancer, ethnicity, and energy intake. Statistical tests were two-sided. The strongest association was with processed meat; those in the fifth quintile of daily intake (g/1000 kcal) had a 68% increased risk compared with those in the lowest quintile (relative risk = 1.68, 95% confidence interval = 1.35 to 2.07; P trend <0.01). The age-adjusted yearly incidence rates per 100,000 persons for the respective quintiles were 41.3 and 20.2. Intakes of pork and of total red meat were both associated with 50% increases in risk, comparing the highest with the lowest quintiles (both P trend
There were no associations of pancreatic cancer risk with intake of poultry, fish, dairy products, eggs, total fat, saturated fat, or cholesterol. Intake of total and saturated fat from meat was associated with statistically significant increases in pancreatic cancer risk but that from dairy products was not. In conclusion, red and processed meat intakes were associated with an increased risk of pancreatic cancer. Fat and saturated fat are not likely to contribute to the underlying carcinogenic mechanism because the findings for fat from meat and dairy products differed. Carcinogenic substances related to meat preparation methods might be responsible for the positive association.

**Radiology 2005; 237(1):322-8.**
(PMID: 16126927)

**Liver and spleen volumetry with quantitative MR imaging and dual-space clustering segmentation.**

Farraher SW, Jara H, Chang KJ, Hou A, Soto JA.

Department of Radiology, Boston Medical Center and Boston University School of Medicine, Boston, MA, USA.

The purpose of this HIPAA-compliant, institutional review board-approved study was to assess the liver and spleen volumes calculated by using a semiautomated dual-space clustering segmentation technique, as compared with the volumes calculated by using the manual contour-tracing method. The quantitative magnetic resonance (MR) imaging data used as input were computed from images acquired by using a mixed fast spin-echo pulse sequence that was implemented with respiratory triggering. Linear regression analysis was used to assess agreement regarding the volumes calculated by using both segmentation techniques. There was strong agreement regarding the regression parameters for the liver (r=0.98, P<0.001) and the spleen (r=0.99, P<0.001) and the mean percentage volume differences for the liver (1.2%) and the spleen (0.9%). The mean segmentation time per patient was significantly shorter with use of the dual-space clustering method (P<0.001).

**Int J Cancer 2005; 117(1):160-5.**
(PMID: 15880501)

**Suppression of metastasis of human pancreatic cancer to the liver by transportal injection of recombinant adenoviral NK4 in nude mice.**


Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

NK4, a 4-kringle fragment of hepatocyte growth factor (HGF), is an HGF antagonist that also acts as an angiogenesis inhibitor. NK4 strongly inhibits the infiltration, metastasis, and tumor growth of pancreatic cancer. The aim of the study was to evaluate the antitumor effect of adenovirus-mediated NK4 gene transfer to the liver on hepatic metastasis of pancreatic cancer in vivo. We constructed recombinant adenoviral NK4 (Ad-NK4), which encodes a secreted form of human NK4. Intrasplicenic injection of Ad-NK4 induced high and relatively maintained expression of NK4 protein in the liver and suppressed the number and growth of metastatic foci in the liver in a nude mouse model. Microscopically, central necrosis was found even in small metastatic foci in Ad-NK4 treated mice. Immunohistochemical analysis of metastatic tumors showed a remarkable decrease in microvessel density and an increase in the number of apoptotic tumor cells after treatment with Ad-NK4. These results indicate that intraportal injection of Ad-NK4 may be a useful therapeutic modality for the clinical control of hepatic metastasis in pancreatic cancer.
Immune responses to DNA mismatch repair enzymes hMSH2 and hPMS1 in patients with pancreatic cancer, dermatomyositis and polymyositis.


Division of Cellular Signaling, Institute for Advanced Medical Research, Keio University School of Medicine, Tokyo, Japan.

To identify tumor antigens useful for diagnosis and immunotherapy of patients with pancreatic ductal adenocarcinoma, the authors applied a SEREX approach with a cDNA library made from 5 pancreatic cancer cell lines and sera obtained from 8 patients with pancreatic cancer, and isolated total 32 genes, including 14 previously characterized genes and 18 genes with unknown functions. Among these isolated antigens, serum IgG antibodies for 2 isolated DNA mismatch repair enzymes, Homo sapiens mutS homolog 2 (hMSH2) and Homo sapiens postmeiotic segregation increased 1 (hPMS1), were detected in patients with pancreatic ductal adenocarcinoma and dermatomyositis (DM), and polymyositis (PM), but not in sera from healthy individuals. Immunohistochemical study demonstrated that hMSH2 and hPMS1 were over-expressed in pancreatic ductal adenocarcinoma compared to normal pancreatic ducts. These results suggested that hMSH2 and hPMS1 may be useful as CD4+ helper T cell antigens for immunotherapy of pancreatic cancer patients and that serum IgG antibodies may be useful for diagnosis of patients with pancreatic ductal adenocarcinoma and DM/PM.


Comparison of iv contrast-enhanced sonography and histopathology of pancreatic cancer.


Department of Imaging Diagnosis, Ogaki Municipal Hospital, Ogaki, Gifu, Japan.

The authors compared contrast-enhanced sonography findings with pathologic findings in pancreatic cancer to evaluate the ability of contrast-enhanced sonography to depict the pathologic changes associated with pancreatic cancer. Thirty-four patients with pancreatic cancer who underwent surgery were investigated. Sonography was performed with contrast material (Leovist) for all patients before surgery. Pathologic findings were evaluated on the basis of the resected cancer specimens. The authors compared contrast-enhanced sonography findings with pathologic findings. All tumors that were hyperechoic on contrast-enhanced sonography were papillary adenocarcinoma, and all tumors that were hypoechoic on contrast-enhanced sonography were ductal adenocarcinoma. Among ductal adenocarcinomas, five (71.4%) of seven tumors for which the size of the hypoechoic area was unchanged on contrast-enhanced sonography had clear tumor margins with no infiltration or inflammation in the margin. In contrast, all tumors for which the size of the hypoechoic area was reduced on contrast-enhanced sonography had unclear tumor margins with infiltration of cancerous cells and inflammation. Nine (90%) of 10 tumors that showed partial contrast enhancement or a vascular shadow in a hypoechic area had large or medium-sized vessels within a tumor at pathology. In contrast, only one (4.8%) of 21 tumors that did not show the vascular shadow in a hypoechic area had no large or medium-sized vessels in a tumor. In conclusion, contrast-enhanced sonography well reflects the pathologic changes of pancreatic cancer and will provide useful information in a pretreatment evaluation.

Application of proteomic technology in identifying pancreatic secretory trypsin inhibitor variants in urine of patients with pancreatitis.

Valmu L, Paju A, Lempinen M, Kemppainen E, Stenman UH.

Department of Clinical Medicine, Division of Clinical Chemistry, Biomedicum, University of Helsinki, Helsinki, Finland.

Although the analysis of genetic variability has traditionally been performed with molecular genetic techniques, the development of proteomic technology has raised the possibility of analyzing genetic variants at the protein level. This method provides additional information about posttranslational modifications and differences in expression. The authors used mass spectrometry to characterize 3 variants of the peptide encoded by the serine protease inhibitor Kazal type 1 (SPINK1) gene, pancreatic secretory trypsin inhibitor (PSTI). A genetic variant of PSTI, N34S, is associated with the development of pancreatitis. The authors used a quadrupole/time-of-flight hybrid mass spectrometer equipped with an electrospray ionization source to analyze the molecular identity of PSTI purified from the urine of 12 patients with pancreatitis and from 3 controls. They also developed a rapid small-scale capture procedure to isolate and analyze PSTI from small volumes of urine. The mutations responsible for mass shifts of different PSTI variants could be verified. The authors observed differences in the expression of different variants as well as a novel proteolytic fragment of PSTI. Small-scale magnetic bead-mediated immunoaffinity chromatography PSTI enabled easy and rapid purification from small urine volumes, facilitating mass spectrometric analysis with adequate sensitivity. In conclusion, pancreatitis-related PSTI variants occurring at nanomolar concentrations in urine can be detected and quantified by immunoaffinity purification and mass spectrometry. In addition, the N34S variant occurs at higher concentrations than the wild type. This finding casts new light on the possible role of PSTI as a cause of hereditary pancreatitis.


Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis.

Varadarajulu S, Tamhane A, Eloubeidi MA.

Division of Gastroenterology-Hepatology, University of Alabama at Birmingham, Birmingham, AL, USA.

Evaluation of a focal pancreatic mass in the setting of chronic pancreatitis (CP) is a diagnostic challenge. The objectives of the study were to compare the diagnostic yield and accuracy of EUS-guided FNA (EUS-FNA) in the evaluation of pancreatic-mass lesions in the presence or the absence of CP and to identify predictors of CP before EUS-FNA of pancreatic-mass lesions. The study design was analysis of data collected prospectively on all patients with solid pancreatic-mass lesions who underwent EUS-FNA at a tertiary referral center. A total of 282 consecutive patients underwent 300 EUS-FNA procedures of pancreatic-mass lesions over a 3-year period. The diagnostic yield and the accuracy of EUS-FNA was compared between patients with and without CP. CP was defined by the presence of more than 4 EUS criteria. Final diagnosis was adenocarcinoma in 210 (70%), benign disease in 64 (21%), other pathology in 19 (6%), and indeterminate in 4 (2%); 3 patients (1%) were lost to follow-up. CP was noted in 75/300 (25%) patients. A lower sensitivity for EUS-FNA was observed in patients with CP than in those without CP (73.9% vs 91.3%; P=0.02). While patients with CP had a higher negative predictive value (88.9% vs 45.5%; P<0.001), no significant differences were observed for specificity (100% vs 93.8%), positive predictive value (100% vs 99.5%), and accuracy (91.5% vs 91.4%) between those with and without CP. False-negative cytology was encountered in 24 cases: 6/71 (8%) with
CP vs. 18/222 (8%) without CP. Patients with CP required more EUS-FNA passes to establish a diagnosis vs. those without CP (median, 5 vs. 2; P<0.001). On multivariable analysis, age <50 years (P<0.001), male gender (P<0.001), black race (P=0.001), and the absence of jaundice (P=0.005) were significantly associated with CP. The impact of EUS-FNA on long-term clinical management was not analyzed. The impact of individual EUS features of CP on sensitivity of EUS-FNA was not evaluated. By protocol, mass lesions that were benign required more passes to definitively exclude malignancy. The authors concluded that EUS-FNA has a low sensitivity for pancreatic-mass lesions in the setting of CP. This decreased sensitivity can be overcome by performing more numbers of passes at FNA, which improves diagnostic accuracy. Demographic features and clinical presentation are predictive of underlying CP in patients with pancreatic-mass lesions.